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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/898,887	07/03/2001	Raghavan Rajagopalan	MRD-61	2188

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EXAMINER	
LUKTON, DAVID	

ART UNIT	PAPER NUMBER
1654	

DATE MAILED: 05/24/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/898,887	RAJAGOPALAN ET AL.	
	Examiner	Art Unit	
	David Lukton	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 March 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *15-46* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *15-46* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Pursuant to the directives of the response filed 3/20/06, claims 15 and 37 have been amended. Claims 15-46 remain pending. Applicants arguments filed 6/21/05 have been considered and found persuasive in part.

The rejection of claims 15-46 under 35 U.S.C. 112, first paragraph (new matter) is withdrawn; however, the rejection of claims 15-46 under 35 U.S.C. 112, first paragraph (enablement) is maintained.

✦

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it in such full, clear, concise and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 15-46 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are drawn to a method of performing a "photosensitizing procedure".

As explained in a declaration filed 2/25/05, applicants demonstrated a modest effect on the viability of Lewis carcinoma cells *in vitro* in the presence of the compound *para-*

nitrophenyl-*tert*-butyl sulfenate. In the presence of the compound and light, there was a slight decrease in cell viability. It is noted that the compound which was tested does not fall within the scope of the claimed invention. Thus, the first question is whether one could expect similar results *in vitro*, in the event that one of the proteins encompassed by substituent variable "E" were to be conjugated with the sulfenate compound that was tested. A second issue concerns the matter of "administering to a target tissue". The claims encompass administering the compound to the subject orally, by injection and topically, for example. Thus, for example, if a tumor is present in the pancreas, would sufficient compound reach the pancreas to "injure" the target tissue...? And would a quantity of 500 micrograms sulfenate compound per gram of pancreas actually reach the pancreas as suggested by claim 30...? Third, applicants have not actually demonstrated that photosensitization occurs when the sulfenate compound is combined with the Lewis carcinoma cells. The results could be explained by a simple homolytic bond scission (as disclosed in Pasto, *Tet. Lett* **35**, 4303, 1994) followed by abstraction of hydrogen atoms from lipid molecules (of the carcinoma cells) or membrane-bound proteins on the cells. This is not the same as a type I or a type II photosensitization reaction.

With regard to the first point, consider, for example, Bonnett R (*Journal of photochemistry and photobiology. B, Biology*, (1990 Jun) 6 (1-2) 29-37). As discussed therein, compound 7 exhibited considerable activity in a photonecrosis assay, whereas

compounds 1-6 were not very effective. The point is that where photosensitization procedures are concerned, minor changes in structure can eliminate activity. Applicants are proposing to extrapolate from a result obtained with the compound *para*-nitrophenyl-*tert*-butyl sulfenate to compounds in which a protein has been conjugated thereto. What will be the effect of the protein on the photosensitization? One cannot "predict" the outcome.

And even if applicants could show that a conjugate of e.g., neurotensin or cholecystokinin and *para*-nitrophenyl-*tert*-butyl sulfenate exhibited an effect on viability of Lewis carcinoma cells *in vitro* which is similar to that exhibited by the *para*-nitrophenyl-*tert*-butyl sulfenate itself, the next issue would be that of how to "administer" the conjugate to the target tissue. Consider, for example, the following types of cancer:

> breast cancer, prostate cancer, lung cancer, colon cancer, rectal cancer, bladder cancer, Non-Hodgkin Lymphoma, melanomas of the skin, cancer of the Kidney and Renal Pelvis, pancreatic cancer, oral cancer, esophagal cancer, ovarian cancer, thyroid cancer, stomach cancer, brain cancer, multiple myeloma, liver and intrahepatic bile duct cancer, acute myeloid leukemia, chronic lymphocytic leukemia, Hodgkin's Lymphoma, testicular cancer, intestinal cancer, chronic myeloid leukemia, acute lymphocytic leukemia, cancer of the vulva, gallbladder cancer, malignant mesothelioma, bone cancer, joint cancer, cancer of the hypopharynx, cancer of the eye, cancer of the nose, cancer of the ureter, cancer of the peritoneum, gastrointestinal carcinoid tumors, bladder cancer, melanoma, breast cancer, non-hodgkin's lymphoma, ovarian cancer, endometrial cancer, pancreatic cancer, kidney cancer (renal cell), prostate cancer, leukemia, non-melanoma cancer of the skin. Also included are sarcomas and carcinomas, such as the following: fibrosarcoma, myxosarcoma, liposarcoma, chondrosarcoma, osteogenic sarcoma, chordoma, angiosarcoma, endotheliosarcoma, lymphangiosarcoma, lymphangioendotheliosarcoma, synovioma, mesothelioma, ewing's tumor, leiomyosarcoma, rhabdomyosarcoma, colon carcinoma, pancreatic cancer, ovarian cancer, prostate cancer, squamous cell carcinoma, basal cell

carcinoma, adenocarcinoma, sweat gland carcinoma, sebaceous gland carcinoma, papillary carcinoma, papillary adenocarcinoma, cystadenocarcinoma, medullary carcinoma, bronchogenic carcinoma, renal cell carcinoma, hepatoma, bile duct carcinoma, choriocarcinoma, seminoma, embryonal carcinoma, Wilms' tumor, cervical cancer, testicular tumor, lung carcinoma, small cell lung carcinoma, bladder carcinoma, epithelial carcinoma, glioma, astrocytoma, medulloblastoma, craniopharyngioma, ependymoma, pinealoma, hemangioblastoma, acoustic neuroma, oligodendroglioma, meningioma, melanoma, neuroblastoma, retinoblastoma, leukemia, lymphoma, multiple myeloma, Waldenströom's macroglobulinemia, and heavy chain disease.

For example, if one wants to perform a "photosensitizing procedure" on a patient with a liposarcoma, which "E" does one use? Is it a neurotensin receptor binding molecule, or a steroid receptor binding molecule? And if so, which one? Or suppose the patient is suffering from a medullary carcinoma. Does one use a "carbohydrate receptor binding molecule", and if so, which carbohydrate, and which molecule? The specification provides no guidance in this regard. And even if the specification had provided some sort of speculation as to which "E" moieties to use in which circumstances, there would be another issue, which is that if one takes a protein or other compound which has been shown to exhibit binding to a particular receptor, and attaches another substituent to it, loss of activity often results. Thus, even if applicants had provided a list of "target tissues", and an accompanying list of specific "binding molecules" which had been shown (by applicants or by others) to bind to the target tissue in question, the reality is that attaching, e.g., an aryl alkyl sulfenate to that "binding molecule" is likely to result in elimination of binding

efficacy.

Thus, for each of several reasons, one of skill cannot "predict" accumulation of the compounds in a target tissue (as required by e.g., claim 16), and one cannot "predict" efficacy in the photosensitization of the target tissue even if accumulation could be achieved. The specification provides no "working examples" of a compound (falling with the scope of the claimed invention) which can be used in accordance with the claimed invention. And the specification provides no guidance as to which "binding molecules" could be used or should be used for a given target tissue. Accordingly, "undue experimentation" would be required to practice the claimed invention.

In response to the foregoing, applicants have begun by arguing that there are examples in the literature of compounds retaining their affinity for a receptor following conjugation to a dye molecule. That some such examples exist in the literature is not disputed by the examiner. But the question is whether one can "predict" whether or not binding activity will be retained (following conjugation) merely be viewing a structure. For example, Yates, Andrew (*Bioorganic & Medicinal Chemistry Letters* **15**(16), 3758-62, 2005) discloses (page 3761, col 1, paragraph 1) that compound 1 suffered a loss of binding affinity (to the hCB_2 receptor) in excess of 250 fold as a result of conjugating a fluorescent group thereto (forming compound 12). This reference supports a

conclusion of "unpredictability". Success of the claimed invention requires that binding specificity of the "E" moiety be retained following conjugation. Perhaps if the claims were limited to treating skin cancers, and limited also to topical administration (to the affected area), the issue of binding specificity would not be so critical. But the claims encompass causing injury to any target tissue that might be of interest to applicants. All of the internal organs are included. Some claims (e.g., claim 16) specify that the photosensitizer accumulate in the target tissue. One cannot have accumulation without binding specificity. Other claims (e.g., claim 30) require that the level of accumulation in the target tissue reach as high as 500 micrograms per gram of the tissue. Applicants have not even determined if such a level can be achieved in the absence of conjugation, to say nothing of what one can expect after the conjugation. Notwithstanding the foregoing, however, the examiner does not argue that failure is inevitable, only that success is "unpredictable".

As noted above, Bonnett R (*Journal of photochemistry and photobiology. B, Biology*, (1990 Jun) 6 (1-2) 29-37) discloses that while compound 7 exhibited considerable activity in a photonecrosis assay, compounds 1-6 were not very effective. Applicants have attempted to dismiss this by arguing that perhaps this finding is the result of an artifact, or that perhaps a control experiment should have been carried out but wasn't. The examiner does not dispute the assertion that there exist some errors in the conclusions

reached in scientific publications. The examiner does not dispute the proposition that, from time to time, an academic scientist will publish a paper in which the results obtained and the conclusions reached were the result of an artifact or flawed experimental design. The first point however, is that such publications are much more the exception than the rule. Academic scientists can suffer a penalty (e.g., reduced funding) if their publications contain errors. Despite the foregoing, however, there are two additional points. The first is that it is just as likely that it is applicants who have discovered an artifact, or made an error in their experimental design which has led to an invalid conclusion. Were this a debate among academic scientists, one could just send a graduate student into the lab to perform more experiments. But that is not a possibility here. Given that this is as much a legal inquiry as a scientific one, the experimental results provided by Raymond Bonnett, and those obtained by applicants must be taken as correct, unless there is good reason or evidence to show that the conclusions are invalid. Thus, given that applicants are just as likely to have undertaken flawed experiments as Bonnett, this particular argument by applicants is "neutralized".

Next, applicants have questioned the examiner's assertion that the claims require an amount of 500 micrograms or photosensitizer per gram of pancreas actually reaches the pancreas, as required by claim 30. Applicants have traversed by arguing that the

examiner's interpretation of this claim is incorrect. The examiner disagress.

Consider the following three claims:

> *100. A method of causing injury to the pancreas in a mammal comprising administering to the pancreas a photosensitizer according to claim 1 in the amount of 500 micrograms per g of the pancreas.*
>
> *101. A method of causing injury to the pancreas comprising administering to a mammal a photosensitizer according to claim 1 in the amount of 500 micrograms per g of body weight.*
>
> *102. A method of causing injury to the pancreas in a mammal comprising administering to the pancreas a photosensitizer according to claim 1 in the amount of 500 micrograms per g of body weight.*

Claim 100 makes it clear that the intent is to administer the compound such the compound reaches the pancreas at a concentration of 500 micrograms per gram of the tissue. Claim 101 is most reasonably interpreted to mean that for a mammal weighing, e.g., 70 kg, an amount of 35 grams would be administered to the subject, and whatever happens to reach the pancreas is what reaches it. But claim 102 is ambiguous. This claim could be interpreted either way. Claim 102 doesn't recite administering to the mammal, it recites administering to the pancreas. For this reason, there is a good argument to be made that the claim is requiring an accumulation of 500 micrograms per gram of the pancreas. If it is really true that applicants have no intention of requiring accumulation in the pancreas (or any other specific organ) at a level of 500 micrograms per gram of the tissue in question, then applicants would have

no reluctance to amend the claims to make clear that the compound is not being specifically administered to a target tissue in any specific numerical amount, but rather that the compound is being administered to the animal *per se*. The foregoing debate is as much about 112, 2nd paragraph as it is about 112-1st paragraph, but the conclusions drawn with respect to claim interpretations do have ramifications with regard to the 112-1st paragraph (enablement) issue. This is not to say, however, that resolving the 2nd paragraph issue will overcome the 112-1st paragraph issue. If the examiner's interpretation of claim 30 is correct, then one of the enablement issues is quantitative in nature; if applicants' interpretation of claim 30 is correct, then the enablement issues are more qualitative in nature. But either way, the claims require accumulation in the target tissue, a proposition for which evidence is lacking and for which "unpredictability" pervades.

Next, applicants have responded to the examiner's assertion that applicants results could be explained by a simple homolytic bond scission (as disclosed in Pasto, *Tet. Lett* **35**, 4303, 1994) followed by abstraction of hydrogen atoms from lipid molecules (of the carcinoma cells) or membrane-bound proteins on the cells, and that applicants' results do not necessarily demonstration that a type I or a type II photosensitization reaction has occurred. Applicants have argued that Pasto has not conducted any experiments in cells, or with lipids. However, the fact that this may be true does not undermine the examiner's assertion that

applicants have not demonstrated a type I or a type II photosensitization reaction. This is not to say that the sulfenate compounds (to which the claims are drawn) will fail to injure tissue (provided that they reach the target tissue in sufficient amount, and provided that sufficient light can irradiate the tissue in question), only that conclusions regarding type I or a type II photosensitization reactions do not necessarily apply.

Applicants have also responded to the examiner's argument that the specification provides no guidance as to which "E" moieties to use for a given target tissue. Applicants have argued that on page 13, this information is provided. However, with the exception of dihydoxyindolecarboxylic acid for melanoma, applicants' assertion is not correct. For example, on page 13 line 9 it is recited that an unidentified "steroid hormone" can be used for treatment of breast lesions and prostate lesions. However, the term "steroid hormone" encompasses an infinite array of choices. Another example is that of "neurotensin receptor binding molecules" for the treatment of neuroendocrine tumors. This could mean anything. Essentially all that page 13 of the specification conveys is that if a compound binds to a target tissue, then use it. But page 13 of the specification is largely uninformative. The one exception, as indicated above, is dihydoxyindolecarboxylic acid for melanoma. Consider the following claim:

103. A method of injuring melanoma tissue comprising administering a compound of the

following formula to a mammal in need thereof

$$E\text{-}X\text{-}Q\text{-}C(R^1)(R^2)\text{-}C(R^3)(R^4)\text{-}O\text{-}S\text{-}Ar$$

wherein E is dihydoxyindolecarboxylic acid

X is selected from the group consisting of ...

R^1 *is selected from the group consisting of ...*

R^2 *is selected from the group consisting of ...*

R^3 *is selected from the group consisting of ...*

R^4 *is selected from the group consisting of ...*

R^5 *is selected from the group consisting of ...*

Q is ... ...

and exposing the melanoma tissue to light .... with sufficient power and fluence rate to activate the compound to injure said melanoma tissue.

If claim 103 were the claim at issue, the force of the examiner's arguments would be significantly diminished. But there is no such claim at issue.

It is maintained that "undue experimentation" would be required to practice the claimed invention.

✧

Claim 37 is objected to because of a typographical error. The claim recites the following

(lines 3-4):

"administering to a target tissue... a sulfenate **photosensitizerin**..."

Here, the term "photosensitizerin" should be two words, rather than one.

✧

Claims 15-46 are rejected under 35 U.S.C. §112 second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

- Claim 15 is indefinite as to the meaning of a "carbohydrate receptor binding molecule", and for that matter, a "carbohydrate receptor". Applicants have provided a few examples of a "carbohydrate receptor", and examples of compounds that will bind thereto. Such information is of some help in advancing the dialog, but the claim is no less indefinite than it was before.

- Claim 29 recites that "E is associated" with one of the recited biomolecules. What is meant by this? Does this mean that "E" must be present as a complex with one of the recited biomolecules at the time of administration, or does it mean that when "E" is administered (unattached to the sulfenate) to a mammal, that "E" forms a non-covalent association with one of the biomolecules, or is something else intended? What is meant by the assertion that (e.g.) a somatostatin receptor binding molecule is "associated" with a polyol, or that a steroid receptor binding molecule is "associated" with a nucleoside?

- Claim 29 recites that "E" can be "associated" with a dendrimer. One interpretation of this embodiment is that the claimed sulfenate compound is not administered as such, but rather is administered as a conjugate of the dendrimer, such that "E" is bonded to an erstwhile nucleophilic group on the dendrimer. If this is the intention, claim 29 should be written in independent form, and the claim made clear that a conjugate is intended.

- Claim 30 recites that the amount which is "administered to the target tissue" can be as high as 500 mg/kg body weight. What is meant by this? There are principally

two interpretations: (a) a quantity of 500 mg/kg body weight is administered to the subject, and whatever amount of the sulfenate that happens to make it to the target tissue is what ultimately gets there, or (b) as much of the sulfenate must be administered as is necessary to reach a concentration of 500 mg/kg within the tissue. Which of these is intended? The same issue applies in the case of claims 31, 40 and 41. Claims 33 and 43 are even more confusing. Are applicants asserting that the intact formulation must come into contact with the target tissue?

- Claim 15 recites that the photosensitizer is administered in a formulation. Thus, the claim mandates that there be at least one other compound or material present. At the same time, however, the claim provides no clues as to what that compound or material might be. Is it water? Is it saline? Is it a pharmaceutically acceptable carrier? The claim provides no clues as to what it is mandating. Claim 36 mandates that the photosensitizer is administered in the form of a cream or gel. Is this independent of the formulation? If one wanted to administer the photosensitizer in the form of a cream, could the formulation itself (excluding the photosensitizer) be in the form of an aerosol, or must they be in the same form? Applicants may hold the view that the answer to this last question should be obvious. At the same time, however, claim 36 does not actually require the photosensitizer and the the formulation itself (excluding the photosensitizer) to be in the same form.

✦

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). The practice of automatically extending the shortened statutory period an additional month upon filing of a timely first response to a final rejection has been discontinued by the Office. See 1021 TMOG 35.

A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED AND ANY

EXTENSION FEE PURSUANT TO 37 CFR 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Lukton whose telephone number is 571-272-0952. The examiner can normally be reached Monday-Friday from 9:30 to 6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang, can be reached at (571)272-0562. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.

DAVID LUKTON, PH.D.
PRIMARY EXAMINER